Design of programmable release formulations for combined therapy

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Abstract: The objective of this work was to develop a multifunctional multiple unit system for programmable release of ketorolac and famotidine. This system employed the novel tablets-in-capsule system and was designed to contain rapid and delayed release minitablets of famotidine with timed release tablets of ketorolac. For maximum gastric protection famotidine was included into two minitablets the first will provide rapid release of the drug (FP0) and the second will be coated with polymers so as to provide a pulse of drug release after a lag time of 6 hours (FL6). For ketorolac the water soluble tromethamine salt was used to develop minitablets providing a pulse of drug release after 1 hour (KL1) with the other minitablet providing sustained drug release after a lag time of 4 hours (KSL4). The later was prepared by developing a minitablet capable of releasing the drug over a period of 4 hours (S4). This was suitably coated to produce KSL4. The study thus developed a programmable release preparation for combined administration of NSAIA and H2 receptor antagonist.

Keywords: Compression coating; Tablets-in-capsule system; Combined therapy; Famotidine; Ketorolac; Controlled release.

INTRODUCTION

Ketorolac is a nonsteroidal agent with powerful analgesic and low anti-inflammatory activity, widely used in the management of both moderate and severe pain [1]. Although oral bioavailability of ketorolac was reported to be 90% with very low hepatic first-pass elimination, the biological half-life of 4 to 6 hours requires frequent administration to maintain the therapeutic effect [2]. The frequent and long-term use of currently available dosage forms of ketorolac may result in gastrointestinal ulceration [3]. To overcome this problem, physicians recommended concurrent administration of antacids with ketorolac. The H2 receptor antagonists such as famotidine which reduce the acid secretion are the most commonly used drugs for this purpose. However, frequent and concurrent administration of multiple unit dose formulations is always hindered by poor patient compliance. Accordingly, the objective of this work was to develop a multifunctional multiple unit system for programmable release of ketorolac and famotidine. This system employed the novel tablets-in-capsule system which was developed by Li and Zhu [4] and
was designed to contain rapid and delayed release minitablets of famotidine with timed release tablets of ketorolac. For maximum gastric protection famotidine will be included into two minitablets the first will provide rapid release of the drug (FP0) and the second will be coated with polymers so as to provide a pulse of drug release after a lag time of 6 hours (FL6). For ketorolac the water soluble tromethamine salt will be used to develop minitablets providing a pulse of drug release after 1 hour (KL1) with the other minitablet providing sustained drug release after a lag time of 4 hours (KSL4). The later was prepared by developing a minitablet capable of releasing the over a period of 4 hours (S4). This was suitably coated to produce KSL4.

The selection famotidine was based on its potency and safety compared to other drugs of the same class. The mechanism of action, pharmacological effects, site of action, and clinical uses are the same as for the other H2-receptor antagonists, but on equimolar bases, famotidine was reported to be about 7.5 and 20 times more potent than ranitidine and cimetidine, respectively, in inhibiting gastric acid secretion. This ensured smaller effective dose of famotidine and hence a suitability for minitablet preparation. In addition, famotidine is relatively free of side effects despite of its high potency [5-7]. Despite of undergoing minimal first-pass metabolism the oral bioavailability of famotidine in man has been reported to be low and variable, ranging from 40% to 50%. This was attributed to its poor aqueous solubility, high polarity, and gastric degradation [8-9]. The poor solubility of this drug suggests that the dissolution rate is the rate-limiting step for bioavailability. Accordingly an optimization of the dissolution of famotidine was necessary before developing the programmed release formulations.

Alternative strategies have been adopted to enhance famotidine dissolution. These included inclusion complex formation with cyclodextrins [10], solid dispersion with polyethylene glycol (PEG) [11] and preparation of liquisolid tablets [12]. Solid dispersion technique will be employed in the current study.

### I. MATERIALS AND METHODS

#### 1. Materials

Famotidine and microcrystalline cellulose (Avicel PH-101) were obtained from Riyadh Pharma Pharmaceutical Co., Saudi Arabia. Ketorolac, Hydroxypropylmethyl cellulose (HPMC) K100M and HPMC E 100 were obtained from Sigma Chemical Co., St. Louis, USA. PEG 6000 was obtained from BDH, Pole, England. Colloidal silicon dioxide (Aerosel 200), sodium starch glycolate and cross-linked polyvinylpyrrolidone were supplied by Tabouk, pharmaceutical Co., Tabouk, Saudi Arabia.

#### 2. Methods

##### 2.1. Preparation of famotidine solid dispersion

The melting method was used to prepare solid dispersions of famotidine with increasing concentrations of PEG 6000. Avicel was included in the solid dispersions to improve their flow characteristics. The prepared solid dispersions included drug, Avicel and PEG 6000 at the ratios of 1:1:1 (FSD1:1), 1:1:2 (FSD1:2) or 1:1:3 (FSD1:3). The PEG was melted on a hot plate (80 °C) before adding the drug with continuous stirring until homogeneity. Avicel was then added with continuous mixing until homogeneity. The dispersions were then left to cool to room temperature whilst mixing to produce the powdered solid dispersions which were passed through a mesh screen with a pore size of 250 μ in diameter.

##### 2.2. Differential Scanning Calorimetry

Thermograms of the samples (Famotidine, PEG and their solid dispersions) were recorded using a differential scanning calorimetry (DSC) DSC-60 (Shimadzu, Japan). Samples equivalent to approximately 2.5 mg of the drug were loaded into aluminum pans and the lids were crimped using a Shimadzu crimer. The thermal behavior of each sample was investigated under nitrogen at a heating rate of 10 °C/min, covering temperature ranges of 25–300 °C. The instrument was calibrated with an indium standard. Data analysis was conducted using the TA-60WS thermal analysis software. The following parameters were calculated:

\[ Tm = \text{transition med point}., \quad \Delta H = \text{the area under the transition peak normalized to the sample weight.} \]

##### 2.3. Preparation of famotidine tablets

##### 2.3.1. Preparation of rapid release minitablet (FP0)

This formulation of FP0 was selected on the basis of the published data [4]. The powdered SD1:1 equivalent to 15 mg famotidine (75% w/w), sodium starch glycolate (10% w/w) and PVP (15% w/w) were geometrically mixed and passed through a 250-m sieve before mixing with talc (0.5%) and Aerosil (0.5%). Tablets (60 mg) were compressed using 5 mm punches.

##### 2.3.2. Preparation of delayed pulse release tablet (FL6)

The FP0 was used as the core in these tablets. These were compression coated using mixtures of Avicel and HPMC K100M at various weight ratios (75:25, 70:30 and 60:40, Avicel/HPMC) with magnesium stearate.
coating process was conducted in two steps. The first step involved filling 60% of the coat into the die. The KP0 tablet was centered in the die followed by slight compression to fix the coating under and around the tablet. The second step involved adding the rest of the coat before compressing the tablets using 5 mm punches.

2.4. Preparation of ketorolac tablets

2.4.1. Preparation of rapid release minitablet (KP0)
As for the FP0 tablets the KP0 minitablets were prepared on the basis of the published data [4]. The powdered drug (10 mg, 75% w/w of the tablet weight), sodium starch glycolate (10% w/w) and PVP (15% w/w) were geometrically mixed and passed through a 250-μm sieve before mixing with talc (0.5%) and Aerosil (0.5%). Tablets (13.5 mg) were compressed using 3 mm punches.

2.4.2. Preparation of delayed pulse release tablet (KL1)
The KP0 was used as the core in these tablets. These were compression coated using mixtures of Avicel and HPMC K100M at different ratios (90:10, 82.5:17.5 and 70:30, Avicel : HPMC), with magnesium stearate (2% w/w) being used as the lubricant system. The weight of the coating system was double the core weight. The coating process was conducted in two steps. The first step involved filling 60% of the coat into the die. The KP0 tablet was centered in the die followed by slight compression to fix the coating under and around the tablet. The second step involved adding the rest of the coat before compressing the tablets using 5 mm punches.

2.4.3. Preparation of sustained release tablet (KS4)
The powdered drug (10 mg, 75% w/w of the tablet weight), HPMC K100M (20%) and Ethylcellulose (5% w/w) were geometrically mixed and passed through a 250-μm sieve before mixing with magnesium stearate (2%). Tablets (13.5 mg) were compressed using 3 mm punches. This formula was prepared and used as the core for the delayed sustained release tablets (KSL4) and it composition was selected so as to provide sustained drug release after rupture of the coat.

2.4.4. Preparation of delayed sustained release tablet (KSL4)
The KS4 was used as the core in these tablets. These were compression coated using mixtures of Avicel and HPMC K100M at various weight ratios (90:10, 80:20 and 70:30, Avicel : HPMC) with magnesium stearate (2% w/w) being used as the lubricant system. The coating process was conducted in two steps. The first step involved filling 60% of the coat into the die. The KS4 tablet was centered in the die followed by slight compression to fix the coating under and around the tablet. The second step involved adding the rest of the coat before compressing the tablets using 5 mm punches.

2.5. Dissolution studies
The dissolution experiments employed the USP XXIV method 2 (paddle method) dissolution apparatus (Electrolab TDT-06P, India). The dissolution medium was distilled water maintained at a temperature of 37 °C with a paddle speed of 100 rpm. The powdered samples (famotidine powder or its solid dispersion) famotidine tablets or ketorolac tablets were added to the dissolution vessels. Samples (5 ml) were taken at predetermined time intervals and immediately replaced with fresh dissolution medium. These samples were immediately filtered through 0.45 μm filters. The first 2 ml of the filtrate were discarded and the samples were assayed for drug content after appropriate dilution with the dissolution medium. The assay employed UV spectroscopy (267 nm for famotidine and 320 nm for ketorolac). The amounts of the drug dissolved at each time point (expressed as % of the total drug added) were plotted as a function of time. These plots reflect the rate of drug release which is good indicator for timed and delayed release formulations. In addition, the cumulative amounts of drug released were plotted as a function of time to produce the dissolution profiles in case powdered samples.

II. RESULTS AND DISCUSSION

1. Preparation and evaluation of famotidine formulations
To prepare timed release formulation it is necessary that the tested drug should have good dissolution characteristics so as to allow the formulator to employ the formulation techniques to develop the required drug release pattern. Famotidine was reported to have low and variable oral bioavailability. This was attributed to its poor aqueous solubility, high polarity, and gastric degradation [8-9]. The poor solubility of this drug suggests that the dissolution rate is the rate-limiting step for bioavailability. Accordingly an optimization of the dissolution of famotidine was necessary before developing the programmed release formulation. The solid dispersion technique which was reported to enhance the solubility of famotidine was employed in the current study. Polyethylene glycol (PEG 6000) which was previously shown to enhance the dissolution of famotidine [11] was employed but Avicel was included with the goal of improving the flowability of the solid dispersion powder.
Table I - Melting transition parameters of famotidine in pure state or as solid dispersion with PEG 6000

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tm (°C)</th>
<th>Enthalpy (J/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure drug</td>
<td>164.0 (0.4)</td>
<td>139.1 (1.2)</td>
</tr>
<tr>
<td>FSD1:1</td>
<td>148.2 (1.4)</td>
<td>62.3 (2.1)</td>
</tr>
<tr>
<td>SD1:2</td>
<td>131.1 (1.7)</td>
<td>33.6 (1.9)</td>
</tr>
<tr>
<td>SD1:3</td>
<td>123.5 (1.1)</td>
<td>20.3 (2.7)</td>
</tr>
</tbody>
</table>

Values between brackets are SD, n = 3.

Figure 1 shows examples of the DSC traces of pure drug, pure PEG 6000 and their solid dispersions. The parameters calculated for the melting transitions are presented in Table I. The pure drug showed sharp endothermic peak at 164 °C followed by a broad exothermic peak at 199.9 °C (Figure 1 and Table I). The endothermic peak corresponds for the melting transition of the drug but the exothermic can be attributed to possible recrystallization or decomposition of the drug. The recorded thermogram is similar to the previously reported results [11]. Preparation of famotidine in the form of solid dispersion with PEG broadened the endothermic peak and reduced the enthalpy and the Tm of the drug. This reduction was increased by increasing the ratio of the polymer in the solid dispersion. In addition to these effects on the main endothermic peak, solid dispersion formation increased the Tm of the exothermic peak from 199.9 °C in case of pure drug to 207.2 °C, 212 °C and 217.6 °C in cases of FSD1:1, FSD1:2 and FSD1:3, respectively. The recorded effects on the melting endothermic peak of the drug can be attributed to possible reduction in the crystallinity of the drug, eutectic mixture formation or possible interaction between the drug and the polymer. X-ray diffraction of famotidine or its solid dispersion with PEG 6000 revealed no change in the diffraction pattern of the drug after its formulation as solid dispersion [11]. This finding excluded the reduction in the crystallinity of the drug. The authors explained the recorded changes in the thermogram of the drug on the basis of possible hydrogen bonding between the drug and PEG. Another possible explanation may depend on the possibility of eutectic mixture formation but the recorded increase in the Tm of the exothermic peak is in the favor of possible hydrogen bonding. The extent of interaction increased with increasing the PEG concentration in the solid dispersion.
Figure 2 shows the dissolution profile of famotidine powder and solid dispersions with PEG 6000. The data reflected poor drug dissolution as indicated from the dissolution profile of the pure drug powder. Incorporation of the drug in solid dispersion formulations resulted in a significant increase in the drug dissolution. There was no significant differences between the dissolution efficiency obtained from different solid dispersions. Accordingly, the solid dispersion containing the smallest proportion of the polymer was selected for preparation of the programmable release formulations.

Figure 2 - The dissolution profile of famotidine powder or solid dispersions with PEG 6000.

Figure 3 shows the release data of famotidine obtained from rapid release minitablet (FP0) or delayed pulse release tablets (FL6). The FP0 was able to release most of the drug within the first 30 minutes ensuring rapid drug effect with the results that the acid secretion is reduced to minimize the stomach irritating effect of the anti-inflammatory drug. For sustained stomach protection the drug was also formulated in a delayed pulse release tablet. This tablet was developed by compression coating of the FP0 using mixtures of Avicel and high viscosity HPMC K100M at various ratios. A coat comprising Avicel and HPMC K100M at a ratio of 75:25 was found optimum for preparing tablets which release the drug after a lag time of 6 hours (Figure 3). Tablets coated with mixtures containing higher proportions of HPMC failed to release significant amounts of the drug even after 8 hours (Figure 3).

Figure 3 - The famotidine release data obtained from immediate release tablet (FP0) and the delayed pulsed release tablet (FL6).
2. Preparation and evaluation of ketorolac formulations

The water soluble derivative, ketorolac tromethamine was used in the current study. For maximum gastric protection it was necessary to have famotidine released before or at least simultaneously with ketorolac. Preparation of the immediate release ketorolac tablets (KP0) resulted in very rapid drug release with most of the drug being released in the first few minutes (Figure 4). Accordingly, an attempt was made to delay the release of the drug. This attempt included the preparation of delayed pulse release tablet with a lag time of 1 hour (KL1). To achieve this, the KP0 was compression coated using mixtures of Avicel and low viscosity HPMC E100 at different weight ratios. Using these mixtures in a ratio of 82.5:17.5 (Avicel-HPMC) produced a tablet with delayed pulse release properties. The lag time was more than 30 minutes. The pulse of the drug release was obtained after 45 minutes (Figure 4). This formulation was considered acceptable taking into consideration that the FP0 releases most of famotidine in the first 30 minutes (Figure 3). Coadministration of both systems can thus ensure rapid analgesic effect with simultaneous gastric protection.

![Graph](image1)

![Graph](image2)

**Figure 4** - The ketorolac release data obtained from immediate release tablet (KP0) and the delayed pulsed release tablets (KL1) which contained Avicel and HPMC E100 at different ratios.
For extended analgesic effect the delayed sustained release tablet of ketorolac was prepared. This tablet was intended to provide sustained drug release after a lag time of 4 hours. To achieve this, a sustained release tablet (KSL4) was developed. This was conducted by mixing the drug with high viscosity HPMC and ethylcellulose. This tablet was able to provide sustained drug release over a period of 4 hours. To obtain the necessary lag time, the sustained release tablet (KS4) was developed. This was conducted by mixing the drug with high viscosity HPMC and ethylcellulose. This tablet was able to provide sustained drug release over a period of 4 hours. To obtain the necessary lag time, the sustained release tablet (KS4) was compression coated using mixtures of Avicel and high viscosity HPMC K100M at various weight ratios. A coat comprising Avicel and HPMC K100M at a ratio of 80:20 was found optimum for preparing tablets which release the drug after a lag time of 4 hours. The drug started to release after a lag time of 4 hours with the release being sustained over a period of 4 hours after the lag time (Figure 5). This lag time was selected based on the short plasma half life of ketorolac taking into consideration that the drug will be released gradually to compensate for the eliminated drug. Formulation coated with a system containing lower HPMC released the drug after a shorter lag time (Figure 5). Tablets coated with the highest concentration of HPMC failed to release significant amounts of the drug during the sampling period.

The compression coating technique was employed successfully in the current study with mixtures of Avicel with HPMC being the main components. Different grades of HPMC were employed as press-coating agents for preparation of delivery systems containing drugs with different solubility. These systems were able to provide chronotherapy for treatment of diseases which attack patients early in the morning [13-15]. These studies revealed that increasing the level of high viscosity HPMC in the coating system extended the lag time and extended the release in vitro and in vivo. Double compression with HPMC was investigated to develop a multiple unit system packed into hard gelatin capsules. Programmable release system was developed by appropriate combination of uncoated and coated minitablets [4]. Compression coating with hydroxyethyl cellulose as the hydrophilic swelling polymer was used and the lag time depended on the thickness of the coat and the particle size. Higher porosity which is associated with larger particles was found responsible for shorter lag time. The authors recorded comparable data with respect to the lag time after in vivo evaluation in healthy human volunteers [16-17]. Despite of successful application of the tablet in capsule system to deliver multiple unit systems with programmable release [4], other investigators incorporated the multiple unit dosage forms (minitablets) into a bigger tablet [18].

In conclusion compression coating and tablet in capsule techniques can be tailored to provide programmable drug release. The developed combinations ensured sustained analgesic effect with sustained gastric protection. For the gastric protection the second pulse of famotidine was delivered after a lag time of 6 hours. This lag time was also selected on the bases of both elimination and pharmacodynamic half life of famotidine.

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REFERENCES


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